REMARKS

Claim Amendments

Claims 5-7, 10-11, 13-14, 19-20, 25-27, 30-33, 38, 40, 49-52, 54, 68, and 74 have been amended and claims 78-83 have been added as shown. Claims 34 and 48 have been cancelled.

Claims 68 and 74 have been amended for clarity and to specify an embodiment wherein the short-term formulation of interferon is not released from the internally presented implantable pump from which the long-term formulation is released. Such amendments are supported by paragraphs [0056] and [0062] of the specification as filed, as well as originally filed claims 37 and 39.

Claims 5-7, 10-11, 13, 19, 25-27, 30-33, 38, 40, and 54 were amended for clarity and for consistency of language.

Claim 14 was amended and new claim 79 was added to clarify the previously pending claim language of claim 14.

Claims 49-52 were amended to correct claim dependency.

Claims 20 was amended and new claims 78, 82, and 83 were added to specify a preferred embodiment wherein the long-term formulation is an omega interferon.

New claims 80-81 have been added to specify particularly advantageous time periods over which the long-term formulation may be released from the pump. Support for such claims can be found at paragraphs [00112] and [00114] of the specification as filed.

No new matter is introduced by the amendments presented herein. Entry of the amendments is therefore respectfully requested. After entry of the amendments, claims 2-17, 19-20, 22, 24-33, 35-38, 40-47, 49-54, and 68-83 are pending.

35 U.S.C. § 103(a)

The pending claims were rejected under 35 U.S.C. § 103(a). Art cited against the various claims include U.S. Patent 5,207,752 ("Sorenson"), directed to a delivery system and method utilizing an external pump, U.S. Patent 6,436,091 ("Harper"), directed to an osmotic pump having a series of barriers that may be breached by a lancet to alter flow rate, and Palmeri *et al.*,

J.Chemotherapy 1990, vol. 2(3), pp. 327-330 ("Palmeri"), directed to administration of alpha2A for colon cancer, as well as Johnson *et al.*, Scientific American, May 1994, pp. 68-75 ("Johnson"), directed to treatment of different diseases with interferons, and U.S. Patent No. 4,847,049 ("Kwan"), directed to alpha interferon formulations with thimerosol.

Applicant continues to maintain that the cited art does not support an obviousness rejection of the claims. Section 103(a) precludes the grant of a patent only if "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains." 35 U.S.C. § 103(a). The Patent Office bears the initial burden of establishing a case of *prima facie* obviousness. *In re Bell*, 26 USPQ2d 1529, 1530 (Fed. Cir. 1993); *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1998); MPEP § 2142. If the Patent Office does not establish a *prima facie* case, the Applicant is under no obligation to submit evidence of nonobviousness, and the rejection must be withdrawn. *Id.*

To establish a proper *prima facie* case, three criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation that the modification or combination would be successful. Third, the prior art reference (or references when combined) must teach all the limitations of the rejected claims. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based upon Applicant's disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991), *citing In re Dow*, 5 USPQ2d 1529 (Fed. Cir. 1988); MPEP § 2142.

As noted previously by Applicant, the Office has utilized in its rejections references which are very distinguishable from Applicant's invention and which cannot be properly combined to arrive at the claims of the instant invention. The Office contends that Applicant has improperly argued against the references individually although they were cited by the Office not individually but in combination to support an obviousness rejection. Applicant understands that the references were used in combination to support rejections under § 103(a) and submits that they have merely been discussed in turn in prior responses and not in the context of individually

supporting claim rejections; Applicant contends, nonetheless, that the references are so distinct from Applicant's invention that even if a suggestion or motivation to combine the references could be found, the combination of the references would not lead to Applicant's invention. Applicant does not suggest, however, that the proper motivation is available in the references.

As an initial matter, claims 2, 3, 8, 10, 14-17, 19, 22, 24, 28, 30, 34-38, 40-54, and 68-73 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Sorenson in view of Harper and Palmeri. According to the Patent Office, the Sorenson patent teaches a method for introducing a therapeutic agent at a first level and then introducing the agent at a second level, in order to achieve and maintain optimal drug levels. Palmeri is relied upon by the Office to show the need for optimization. Palmeri discloses modulation of interferon $\alpha 2a$ to reduce side effects and administration of different levels of interferon to achieve an optimal dosage. Harper teaches osmotic, implantable pumps that can be useful in optimization, according to the Office.

As noted above, in determining *prima facie* obviousness, the Patent Office must consider whether the cited references teach all the limitations of the claims of the invention. Applicant submits that, contrary to the position taken by the Office, the combination of the three references does not lead one to each and every limitation of Applicant's claimed invention. In particular, the Office has relied on Sorenson and Harper and Palmeri to reject independent claims 68, 74, and 41.

The external, iontophoretic pump taught by Sorenson is designed for transdermal delivery of therapeutic agents. Electrodes are utilized to provide an initial high current to drive an agent into the body, ensuring that the initial drug concentration in the bloodstream reaches a temporary peak value. The delivery of high current may subsequently be reduced or halted for some period to allow for the drug concentration to subside to a maintenance level. The pump taught by Sorenson may then be stepped up by application of appropriate delivery of current to again increase the drug concentration, such as with a user-activatable timer. Sorenson's device is especially useful in a situation where a painkiller is administered to the patient and the scheme allows rapid input of drug to the bloodstream. The method of delivery taught by Sorenson is intended to provide the patient with an initial high peak level of drug concentration, followed by lower maintenance levels.

As pointed out by Applicant in an earlier response, Sorenson's pump is not an internally presented implantable pump. The disclosure of Sorenson very clearly encompasses an *external* iontophoretic pump useful for delivery of drugs across intact skin. The pending independent claims of the instant application clearly call for an *internally presented implantable pump* that is *not externally programmed.* Sorenson, by contrast, teaches programming of the pump with particulars regarding delivery. Sorenson's apparatus is highly distinguishable from that of Applicant. Sorenson's method, too, is distinct from that of Applicant. Sorenson provides the patient with an initial high peak level of drug concentration, followed by lower maintenance levels, whereas the instant invention utilizes a short-term formulation to find a suitable dose that provides an appropriate level of therapeutic benefit for the patient and enables dose-individualization and the setting of a long-term administration scheme. The short-term formulation is not boosted up to a peak level, then allowed to drop off, and then stepped up further, as taught by Sorenson. The Office contends, however, that Sorenson has been relied upon not for its pump but for teaching optimizing, whereas the Harper patent has been utilized to show an implantable pump. Such reliance still fails to meet the Office's burden, as discussed further below.

Harper teaches an implantable osmotic pump, optionally with a catheter system, having a series of impermeable and semipermeable barriers. The semipermeable barriers can be breached, as with a lancet, to alter the flow rate from the pump once the device has been implanted in the patient.

Even if one were to find the requisite motivation to combine Sorenson with Harper and additionally with Palmeri, which teaches identification of a maximally tolerated dose of recombinant alpha interferon 2a with 5-fluorouracil in a treatment of advanced colorectal carcinoma, and downward adjustment of doses prompted by ill effects in patients, *each and every* limitation of the pending claims is not presented in the cited art. Applicant's claims 68 and 74 include the step of "adjusting the dosage with the short-term formulation to increase therapeutic response." In claim 68, this is followed by the step of "subsequently selecting a dosage to be administered as a long-term formulation [having] a controlled rate of release over time." In claim 74, this is followed by the steps of "determining the most commonly identified

optimal dosage over time in a sufficiently large population of the animals to define such dosage as a unit dose," "subsequently, defining a long-term formulation for delivering such dosage over time as more unit-dose or a fraction thereof, such that, in aggregate, the optimal dosage identified during dosing with the short-term formulation can be approximated with the unit-dose or fractional unit-dose combination using the long-term formulation to deliver the interferon in a controlled dose over time," and "selecting a dosage to be administered to an individual animal with a long-term delivery." Thus, independent claim 68 has an adjusting step followed by a selecting step and independent claim 74 has an adjusting step followed by determining, defining, and selecting steps, all of which are to occur prior to administration of the long-term formulation. The prior art absolutely does not teach nor suggest such steps.

Applicant grants that the method of using the iontophoretic pump taught by Sorenson includes the step of making some adjustments. While Sorenson may teach or suggest some sort of optimization, such teaching or suggestion is not sufficient to arrive at the claimed invention because Sorenson does not teach or suggest the form of optimization applicable to Applicant's methods. A teaching of optimization in the context of an external iontophoretic pump that aims for a high initial peak value followed by a later maintenance dose is not relevant to methods for the treatment of an interferon-responsive disorder or for individualizing doses of interferon as taught by Applicant, wherein administration of a short-term formulation is utilized to optimize a later administered long-term formulation released via an implantable long-term delivery device. Sorenson provides one of ordinary skill in the art with no guidance on the optimization, and particularly the adjusting and selecting/determining/defining steps in the methods of the invention.

Although not specifically noted for this purpose by the Office, Applicant notes that the method of using the osmotic pump taught by Harper also includes discussion of making some adjustments. Applicant disagrees, however, that the Sorenson and Harper references, whether in combination or even if considered individually, suggest the adjusting or selecting, determining, and defining steps of the invention. For instance, according to claim 68, one practicing the method of the invention is to administer a short-term formulation for interferon and adjust the short-term formulation dosage as appropriate. The information regarding the administration of the short-term formulation is utilized to subsequently select a long-term formulation dosage and

thereafter administer it. As noted in the disclosure at paragraphs [0030], [0036], and [0067], and in claims 14 and 34, the subsequent selecting and administering of the long-term formulation may occur at a time period removed, perhaps even substantially removed, from the steps of administering the short-term formulation and adjusting to increase therapeutic response. None of the references cited suggest such limitations and therefore a *prima facie* obviousness rejection has not been made.

One following the Sorenson teachings may be inclined to rapidly administer a drug, *e.g.*, by using high current to input a drug into the bloodstream through a dermal barrier, and thereafter to effectively turn down a knob and pull back from the peak level spike for a maintenance dose of the drug. The current may be stepped up later, presumably as the effects of the initial influx and maintenance dose wear off, if needed. This mode of operation is understandable given that the pump and method of Sorenson is designed for materials such as painkillers, which are well-suited to a rapid influx to an initial peak level for immediate relief to the patient, followed by a reduction to a lower level steady dose, so that the patient does not receive any more of the painkiller than is required in the situation. One following Sorenson would not, however, administer a short-term formulation and make adjustments and selections for a later administered, dose-optimized long-term formulation. Instead, a follower of Sorenson's teachings would typically make a reduction in a secondary dosage level, at least for some period of time, whereas one following the teachings of the invention would not necessarily make a reduction and may in fact make an upwards adjustment to increase therapeutic response. Although Sorenson suggests that a later "step up" in dosage is possible, *e.g.*, through the use of a user-activatable switch, any reliance the Office may place in such a subsequent increase taught by Sorenson cannot be considered to be the same sort of adjustment step taught by Applicant's disclosure. Applicant's adjustment is of the *short-term formulation* and is designed to ascertain a suitable dosage for later long-term administration via an internally presented implantable pump that is not externally programmed, whereas Sorenson's adjustment is necessarily a turning down or up of a controller of electric current so that the amount of a particular drug formulation passing through the skin into the bloodstream of the patient is varied per the needs of the patient at any given time. Further, as noted at paragraph [0020] of the specification as filed, the instant invention has the advantage of minimizing or eliminating "the need to alter the rate or change the

dose-rate of the drug once long-term dosing has commenced with a long-term delivery system." Thus, the adjusting and selecting/determining/defining steps of the invention are of a different nature than the optimizing taught by Sorenson in the art.

The pump and methods of Harper are also lacking in suggesting the adjusting and selecting steps of Applicant's invention. Harper's osmotic pump includes impermeable barriers that may be breached as needed and correlative semipermeable barriers that may be exposed as needed to alter the release rate of a drug from the osmotic pump. This does not mean, however, that one following the teachings of Harper or of Harper and Sorenson together would arrive at the steps of administering a short-term formulation, adjusting that short-term formulation, and subsequently selecting the dosage of the long-term administration or actually administering it. Whatever adjusting is taking place according to Harper's or Sorenson's teachings is clearly not the same type of adjusting that is taught by Applicant.

Sorenson, Harper, and Palmeri taken together would not lead one of ordinary skill in the art to arrive at all limitations of Applicant's invention, even if the requisite motivation to combine the disparate references could be found. Such combination would not lead one to methods of treatment or methods of individualizing doses having short-term and subsequent long-term interferon formulation administration steps, wherein the long-term formulation is released from an internally presented implantable pump that is not externally programmed, as taught in the instant application. Nor would such combination of art lead to a method of manufacture as claimed by Applicant wherein standard and reduced rate long-term delivery devices are prepared and such devices release drug from implantable pumps that are not externally programmed and are suitable for internal presentation.

One must conclude, therefore, that the above three references cited by the Office do not teach each and every limitation of the independent claims and further that the obviousness rejection is improper since the Office has not established its *prima facie* case.

Claims 4-7, 9, 12, 13, 20, 25-27, 29, 32, and 33 were rejected under § 103(a) in view of the Sorenson, Harper, and Palmeri references and further in view of Johnson. Johnson discusses the treatment of various disorders and medical conditions with the use of various types of interferons. Since the obviousness rejection is improper with respect to the independent claims in this case particularly due to the failure of the art to teach each and every limitation of the

claims, Applicant maintains that the rejection of dependent claims based on the Sorenson, Harper, Palmeri, and Johnson references is also improper. One would not find all limitations of the rejected claims in the cited art.

Claims 11 and 31 were also given an obviousness rejection. Kwan, which teaches an interferon formulation including thimerosal, was applied by the Office in combination with Sorenson, Harper, and Palmeri. Claims 11 and 31 specify that in some embodiments the short-term and the long-term formulations differ. The Office states that Kwan is cited as teaching compositions with "advantageous formulations." Although the formulations taught by Kwan may be advantageous for some purpose such as retarding microbial growth, this rejection is meaningless in that Kwan's formulations are not relevant to the scope of claims 11 and 31. In any case, Kwan in combination with the Sorenson, Harper, and Palmeri references fail to make obvious claims 11 and 31 because even if motivation to combine the references were to be found, all claim limitations are not met in the independent claims and Kwan adds nothing to supply the missing limitations. The rejection is therefore improper and Applicant requests that it be withdrawn.

The Office has thus failed to establish a *prima facie* case in this instance. Applicant teaches methods for the treatment of an interferon-responsive disorder or for individualizing doses of interferon or for manufacturing a long-term delivery device. Sorenson and its secondary references fail to teach each and every limitation of Applicant's independent claims. Applicant therefore submits that the currently pending claims are not obvious in light of the Sorenson, Harper, Palmeri, Johnson, and Kwan references and requests that the rejections be withdrawn.

Notably, claim 20 has been amended and new claims 78, 82, and 83 have been added to particularly claim the use of an omega interferon in the long-term formulation. Omega interferon is a preferred embodiment and is well-suited to delivery via a long-term delivery system. These claims are clearly non-obvious in view of the cited references, particularly as the Palmeri reference, which does not utilize an omega interferon, is inapplicable to such claims and the combination of Palmeri with the other cited references fails to teach the limitations recited in the claims.

Adjustments to Claim Language

Although Applicant contends that the Office has erred in applying a § 103 rejection to the claims and that claims 68 and 74 are patentable as presented, Applicant has chosen to make several amendments for clarity and to expedite prosecution. Applicant maintains its argument, nonetheless, that the claims are non-obvious as presented prior to entry of this amendment, and reserves the right to pursue such claims in a later case.

In particular, independent claims 68 and 74 have been amended, as reflected in the Listing of Claims, to recite the further limitation that the short-term formulation of interferon is not released from the internally presented implantable pump from which the long-term formulation is released. As is already evident from the pending claim language, the claim recites that the long-term formulation of interferon is released from an internally presented implantable pump that is not externally programmed. Such separate modes of administration for the short-term and long-term formulations find written description support in Applicant's disclosure. Particularly at paragraphs [0056] and [0062] of the specification as filed, as well as at claims 37 and 39 as originally filed, Applicant presents several modes of administration for the various administration steps and includes separate modes of administration for the short-term and long-term administration steps. An internally presented implantable pump that is not externally programmed is well-suited and highly desirable for administration of a long-term formulation. As previously noted, a key advantage of a long-term delivery system utilizing an implantable pump is keeping it in place in the patient for a prolonged period and allowing for controlled release of the appropriate dose of the drug over that given prolonged time period, thus obviating the need for repeated injections or other types of administrations, keeping the rate of administration of the drug steady, and increasing overall patient compliance with the treatment. Although the administration of the short-term formulation may also utilize such a pump, a higher degree of flexibility in the short-term administration is desirable as a practical matter. Thus, Applicant has made the amendments to claims 68 and 74 to specify that the short term formulation is not released from the internally presented implantable pump from which the long-term formulation is released.

Although not necessary, this amendment also serves to further distinguish the invention from the references applied by the Office. Sorenson and Harper do not contemplate administration of short-term and long-term formulations via different modes of administration.

None of the other cited references contributes any disclosure to meet this shortfall in the prior art.

Accordingly, Applicant submits that the obviousness rejection does not support the claims as presented herein. Therefore, the rejection must be removed by the Office and an indication of the allowability of the claims is warranted.

Conclusion

Applicant submits that the claims as presented above are allowable and early notification to this effect is respectfully requested. The Examiner is invited to telephone the undersigned representative of the Applicant at 415-544-7038 if any issues remain.

Respectfully submitted,

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